J. Physiol. (1963), **165**, *pp.* 266–273
With 4 text-figures
Printed in Great Britain

THE PART PLAYED BY CEREBRAL ANAEMIA IN THE RESPONSE TO OCCLUSION OF THE COMMON CAROTID ARTERIES IN THE CAT

By A. M. BROWN, HELEN N. DUKE and N. JOELS
From the Department of Physiology, Middlesex Hospital Medical School, London, W. 1

(*Received* 1 *June* 1962)

Astley Cooper (1836) first described the rise of systemic arterial blood pressure which occurred as a result of ligation of the common carotid arteries. He ascribed it to the effects of cerebral anaemia, as did Magendie (1838) who confirmed his experimental findings. Throughout the latter part of the nineteenth century the belief persisted that cerebral anaemia directly excited the medullary vasomotor centre. The carotido-cephalic perfusion experiments of Francois-Franck (1877) provided seemingly strong support for this view, for changes in systemic pressure were caused by altering the perfusion pressure in the isolated head.

Hering's experimental results summarized in his monograph (1927) entirely changed this view. Hering (1927), Heymans (1929) and Koch (1931) proved that the carotid sinus was provided with a generous baroreceptor innervation and served as an important reflexogenic zone. The carotid baroreceptors were shown by Bronk & Stella (1932) to be tonically active at normal systemic blood pressures, discharging with every pulse. Heymans, Bouckaert & Dautrebande (1932) placed clips on both the internal and external carotid arteries cranial to the sinus. Though this produced cerebral anaemia there was no rise in systemic blood pressure. The effects of clipping the common carotid arteries were thereafter attributed to the reduction in baroreceptor activity which follows the occlusion.

Von Euler & Liljestrand (1943) and Landgren & Neil (1951) later showed that chemoreceptor excitation due to the reduction of carotid body blood flow caused by occlusion of the common carotid arteries also contributes to the rise in blood pressure.

Somewhat illogically, the effects of cerebral anaemia produced concomitantly with those of altered baroreceptor and chemoreceptor activity by occlusion of the common carotid arteries have since been persistently ignored. We have therefore re-examined the effects of clipping the common carotid arteries. Carotid bypasses have been used so that flow to the sinus regions could be interrupted either with or without simultaneously inter-

fering with the carotid flow to the brain. Our results show that cerebral anaemia undoubtedly enhances the reflex effects caused by occlusion of the common carotid arteries.

METHODS

Cats were anaesthetized by the intraperitoneal injection of chloralose, 90 mg/kg body weight. The trachea was cannulated and the cannula connected to inspiratory and expiratory paraffin valves. A lever, operated by a tambour placed distal to the expiratory valve, qualitatively recorded respiration on a kymograph. Femoral blood pressure was registered by a mercury manometer.

Two groups of experiments were performed. In four cats T cannulae were inserted into both common carotid arteries caudal to the origin of the superior thyroid and dorsal muscular arteries (Fig. 1*a*). The sinus regions were bypassed with polythene tubes which connected the stem of each T cannula to the corresponding external carotid artery, which was ligated between the sinus and the insertion of the bypass. Placing clips on the common carotid arteries just caudal to the T cannulae interfered with the blood flow both to the sinus regions and to the brain. If the clips were applied just cranial to the cannulae only the flow to the sinuses was affected.

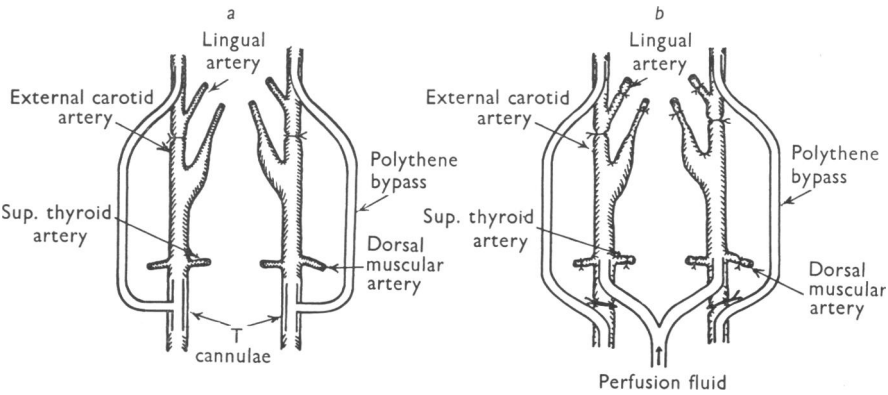

Fig. 1. Diagrams to show arrangement of bypasses. (*a*) Experiments in which the carotid regions were supplied by the animal's own circulation. (*b*) Experiments in which the carotid sinuses and carotid bodies were perfused with Ringer–Locke solution.

In a second group of four animals (Fig. 1*b*) both sinus regions were vascularly isolated by ligation of all the arterial branches arising from the bifurcation, with the exception of those supplying the carotid body. The sinus nerves and the venous drainage of the carotid bodies were carefully preserved. The sinuses were perfused through cannulae in the common carotid arteries with Ringer–Locke solution to which sufficient 'Dextraven' (Dextran injection B.P.) had been added to provide an adequate colloid osmotic pressure. The temperature of the perfusate was maintained at 37° C. The perfusion apparatus has previously been described (Joels, Neil & Vaughan Hudson, 1961).

The perfused sinuses were bypassed with polythene cannulae which connected the common carotid arteries caudal to the insertion of the perfusion cannulae with the corresponding external carotid arteries cranial to the sinus regions. The flow of perfusate to the sinuses and the flow of blood to the brain through the bypasses could thus be arrested independently or simultaneously.

In several experiments a perfusate to which dinitrophenol 1:20,000 had been added was temporarily substituted for the 'control' perfusate. Since this did not alter the perfusion pressure or the flow of perfusate, the effects of cerebral anaemia on the responses to chemoreceptor excitation could be investigated thereby in circumstances where there was no associated alteration in baroreceptor discharge.

RESULTS

Experiments in which T *cannulae were inserted in the common carotid arteries*

When the common carotid arteries were occluded caudal to the T cannulae the blood flow to both the sinus regions and the brain was interrupted, as ordinarily occurs when clips are applied to the common carotid arteries. The characteristic hypertension and hyperpnoea resulted (Fig. 2*a*). When clips were placed on the common carotid arteries just cranial

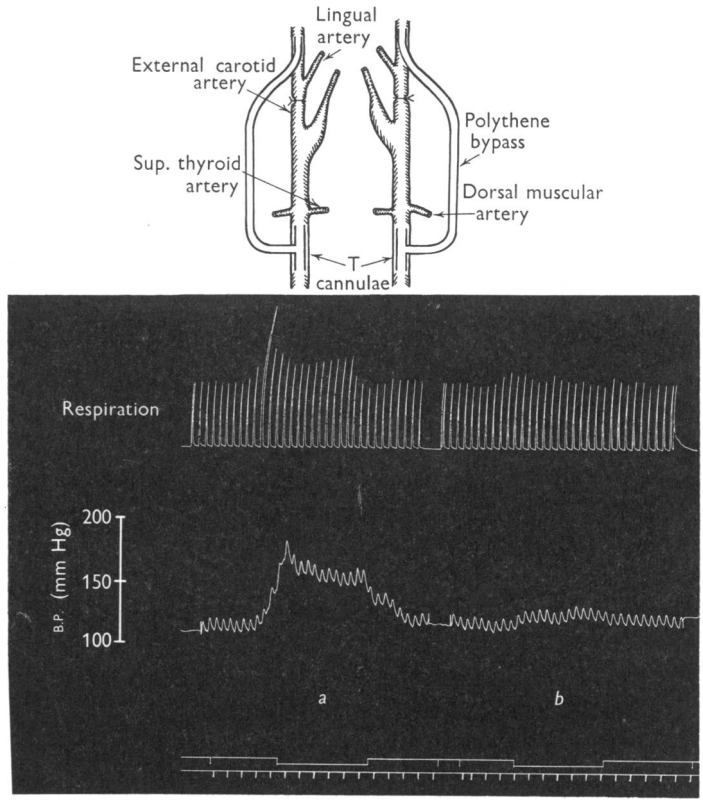

Fig. 2. Records from above downwards: respiration, femoral blood pressure, signal and time marker, 10 sec. Diagram shows experimental arrangement. (*a*) Both common carotid arteries clipped just caudal to the T cannulae, interfering with flow to both the sinus regions and the brain. (*b*) Clips applied just cranial to the T cannulae so that only the flow to the sinuses is affected.

to the T cannulae the increases in the blood pressure and the breathing were quite trivial (Fig. 2*b*). As this procedure interrupted the blood flow to the sinus regions without simultaneously interrupting that to the brain, these results imply that cerebral anaemia is an important factor in the response to carotid occlusion. In some animals flow through the bypasses had less effect on the response. However, the bypasses may not only modify the blood flow to the brain. In the cat there are abundant anastomoses between the carotid and vertebral circulations. Chungcharoen, Daly, Neil & Schweitzer (1952) have shown that when both common carotid arteries are clipped there is an immediate fall in intrasinusal pressure, followed by a partial recovery due to blood flowing back into the sinus through these anastomotic channels. When, as in the experiment shown in Fig. 2*b*, the common carotid blood flow to the brain continued through the patent bypasses, the back-flow into the sinuses may have been even greater than normally occurs after clipping the common carotid arteries. This might account for the very small responses seen when the common carotid arteries were occluded cranial to the T cannulae.

Perfusion of the vascularly isolated, innervated carotid bifurcation entirely avoids such complications and permits a more elective analysis.

Experiments in which the carotid bifurcations were perfused

When the perfusion was turned off the pressure in the sinuses steadily fell from its initial value of 110 mm Hg as the fluid escaped through the venous drainage of the carotid body, reaching 40 mm Hg after about 15 sec. When shutting off the perfusion was combined with cerebral anaemia produced by simultaneously clipping the common carotid arteries caudal to the bypasses, a rise of blood pressure and stimulation of respiration resulted (Fig. 3*a*). If the perfusion was turned off and cerebral flow allowed to continue via the bypasses (Fig. 3*b*) the cardiovascular and respiratory responses were less marked, and moreover commenced after a longer latent period. Cerebral anaemia alone, produced by occlusion of the common carotid arteries caudal to the bypasses while perfusion of the carotid bifurcations continued, was virtually without effect on the circulation or respiration (Fig. 3*c*). Similar effects were seen in all the animals in this group of experiments.

Even though it had little effect by itself, the reduction in cerebral blood flow caused by shutting the carotid bypasses thus increased the reflex effects of the alterations in carotid baroreceptor and chemoreceptor activity which followed interruption of the perfusion.

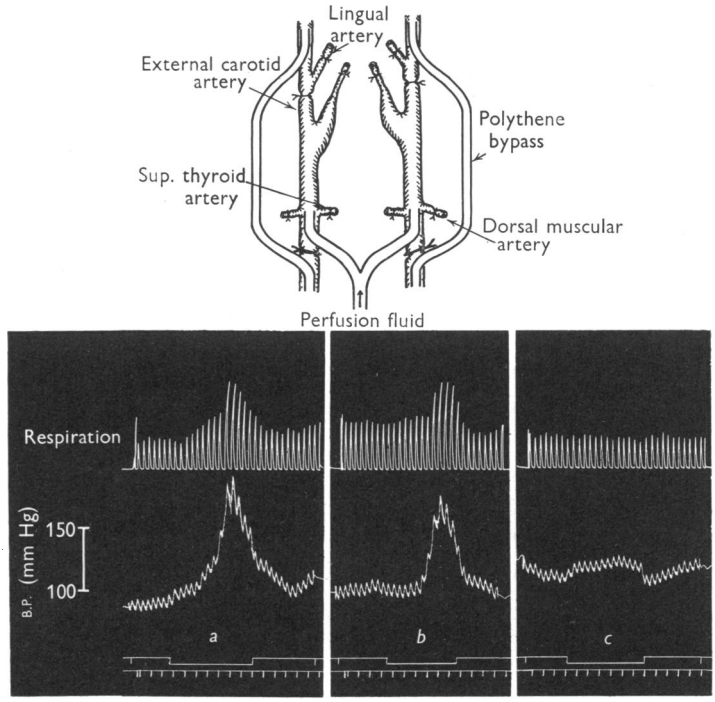

Fig. 3. Records from above downwards: respiration, femoral blood pressure, signal and time marker, 10 sec intervals. Diagram shows experimental arrangement. (*a*) Perfusion turned off and both common carotid arteries clipped caudal to bypasses, i.e. cerebral flow reduced. (*b*) Perfusion turned off, common carotid arteries not clipped. (*c*) Common carotid arteries clipped caudal to bypasses, flow of perfusate continued unchanged.

Cerebral anaemia and chemoreceptor reflex responses

Jarisch, Landgren, Neil & Zotterman (1952) have shown that dinitrophenol (DNP) evokes a brisk discharge from the glomus chemoreceptors. Replacing the normal perfusate by a perfusate containing DNP 1:20,000 while maintaining the same steady perfusion pressure thus excited the chemoreceptors without at the same time altering baroreceptor activity. The influence of cerebral anaemia on purely chemoreceptor reflexes could then be studied.

In the experiment shown in Fig. 4 the sinus regions were perfused throughout. Replacement of the 'control' perfusing fluid by one containing DNP 1:20,000 caused reflex hypertension and hyperpnoea, particularly when the carotid bypasses were simultaneously occluded (Fig. 4*a*). When the carotid bypasses were left patent the same chemoreceptor stimulus produced only feeble reflex responses (Fig. 4*b*). Occlusion of the carotid

bypasses caused negligible effects (Fig. 4*c*) when the carotid bodies were perfused with control fluid (and were therefore not stimulated). Hence cerebral anaemia increases the reflex responses to stimulation of the chemoreceptors alone.

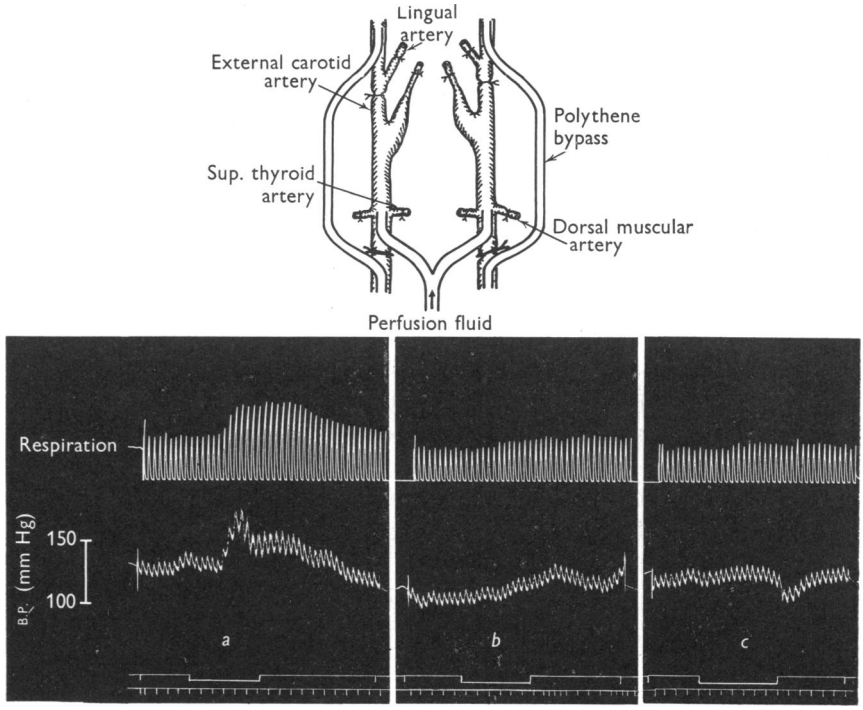

Fig. 4. Records from above downwards: respiration, femoral blood pressure, signal and time marker, 10 sec. In all three records flow of perfusate to sinus regions continued throughout. (*a*) During period indicated by signal DNP 1:20,000 substituted for control perfusate and common carotid arteries simultaneously occluded caudal to bypasses. (*b*) DNP 1:20,000 substituted for control perfusate, common carotid arteries not occluded. (*c*) Both common carotid arteries occluded caudal to bypasses, sinus regions perfused throughout with control fluid.

DISCUSSION

There is no doubt that occlusion of the common carotid arteries reduces the cerebral blood flow in the cat. Vertebral artery blood flow may be increased by cutting off the external carotid contribution to the circle of Willis. The reflex rise of pressure induced by the occlusion may contribute to this increase. Nevertheless, applying clips to the common carotid arteries of the cat must deprive the brain of the major fraction of its blood supply (Chungcharoen *et al.* 1952).

It is indeed surprising that occlusion of the carotid bypasses does not

produce any cardiovascular or respiratory disturbance itself. The present results reveal, however, that when cerebral anaemia accompanies the onset of chemoreceptor stimulation, as is produced by occlusion of the common carotid arteries, it considerably increases the reflex effects thereof. In the absence of this reduction in cerebral flow the responses are either considerably reduced or even quite trivial.

These observations have been made in the cat, in which the carotid system makes an especially large contribution to cerebral blood supply. In other species the carotid system may supply a smaller fraction of cerebral blood flow and cerebral anaemia may not enhance the effects of carotid occlusion to so great a degree. M. de Burgh Daly and J. L. Hazzledine (personal communication) have recently perfused the sinuses in the dog, bypassing the sinus regions by cannulae connecting the common carotid with the external and internal carotid arteries. In this species, in which the vertebral and anterior spinal arteries make a relatively greater contribution to cerebral blood supply than in the cat, the reflex circulatory and respiratory responses to carotid body stimulation were little affected by the arrest of the common carotid flow to the brain.

However, there is little doubt that in the cat the responses to carotid occlusion cannot be regarded simply as the effects on the medullary centres of the withdrawal of baroreceptor discharge and of increased chemoreceptor activity. Consideration must also be given to the fact that these afferent streams are converging on centres whose responses are enhanced by the simultaneous reduction in cerebral blood flow.

SUMMARY

1. Occlusion of the common carotid arteries not only interferes with the blood flow to the sinus regions, but also affects the carotid contribution to cerebral blood flow.

2. By providing suitable bypasses it has been possible to interfere with the flow to the normally vascularized or perfused carotid sinus regions with or without at the same time altering the blood flow to the brain.

3. In the absence of reduced cerebral blood flow the alterations in baroreceptor and chemoreceptor activity provoked by clipping the common carotid arteries are followed by much smaller changes in the blood pressure and breathing. Thus cerebral anaemia normally increases the response to occlusion of the common carotid arteries.

4. Cerebral anaemia has similarly been shown to enhance the effects of elective stimulation of the carotid body chemoreceptors.

We wish to acknowledge the guidance and advice given us by Professor E. Neil, at whose instigation this research was undertaken. One of us (A.M.B.) was the holder of a Life Insurance Medical Research Fellowship.

REFERENCES

BRONK, D. W. & STELLA, G. (1932). Afferent impulses in carotid sinus nerves; relation of discharge from single end organs to arterial blood pressure. *J. cell. comp. Physiol.* **1**, 113–130.

CHUNGCHAROEN, D., DALY, M. DE B., NEIL, E. & SCHWEITZER, A. (1952). The effect of carotid occlusion upon the intrasinusal pressure with special reference to vascular communications between the carotid and vertebral circulations in the dog, cat and rabbit. *J. Physiol.* **117**, 56–76.

COOPER, A. (1836). Some experiments and observations on tying the carotid and vertebral arteries and pneumogastric, phrenic and sympathetic nerves. *Guy's Hosp. Rep.* **1**, 457–475.

FRANCOIS-FRANCK, C. A. (1877). Recherches sur l'influence que les variations de la pression intra-cranienne et intra-cardiaque exercent sur le rhythme des battements du cœur. *Trav. lab. Marey*, **3**, 273–292.

HERING, H. E. (1927). *Die Karotissinus Reflexe auf Herz und Gefasse.* Leipzig: Steinkopff.

HEYMANS, C. (1929). Le sinus carotidien, zone réflexogène régulatrice du tonus vagal cardiaque du tonus neurovasculaire et de l'adrénalinosécrétion. *Arch. int. Pharmacodyn.* **35**, 269–306.

HEYMANS, C., BOUCKAERT, J. J. & DAUTREBANDE, L. (1932). Weitere Untersuchungen über die Blutdruckzügler und die reflektorische Atmungsregulation durch innere Druck- und chemische Reize. *Pflüg. Arch. ges. Physiol.* **230**, 283–298.

JARISCH, A., LANDGREN, S., NEIL, E. & ZOTTERMAN, Y. (1952). Impulse activity in the carotid sinus nerve following intra-carotid injection of potassium chloride, veratrine, sodium citrate, adenosine-triphosphate and α-dinitrophenol. *Acta physiol. scand.* **25**, 195–211.

JOELS, N., NEIL, E. & VAUGHAN HUDSON, B. (1961). The investigation of chemoreceptor responses from the perfused carotid body in the cat. *J. Physiol.* **155**, 30–32*P*.

KOCH, E. (1931). *Die reflektorische Selbsteuerung des Kreislaufes.* Leipzig: Steinkopff.

LANDGREN, S. & NEIL, E. (1951). The contribution of carotid chemoreceptor mechanisms to the rise of blood pressure caused by carotid occlusion. *Acta physiol. scand.* **23**, 152–157.

MAGENDIE, F. (1838). *Leçons sur les phénomènes physiques de la vie.* Vol. 3. Bruxelles.

VON EULER, U. S. & LILJESTRAND, G. (1943). The role of the chemoreceptors of the sinus region for the occlusion test in the cat. *Acta physiol. scand.* **6**, 319–323.